REMARKS

Status of the claims

Claims 1 - 11 have been examined.

Claims 1 - 11 are canceled herein.

New claims 12 - 45 are added by amendment herein and are presented for further examination.

Support for new claims 12 - 45 can be found throughout the specification as filed, including the original claims; no new matter has been added.

Written Description Rejections Have Been Obviated By Amendment And Should Be Withdrawn

The Examiner rejects claims 1 - 5 under 35 U.S.C. 112, first paragraph, for inadequate written description support for the generic phrase "a rescue agent"; claims 6 - 11, drawn with specificity to use of uracil as the rescue agent, are free of the rejection.

Applicant respectfully traverses the rejection. Solely to expedite prosecution, however, and explicitly reserving the right to prosecute claims of the original scope in one or more continuation applications, applicant has canceled all pending claims; all claims newly added by amendment herein are drawn to topical use of uracil, thus obviating the rejection.

The rejection having been obviated, applicant respectfully requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 103
Are In Error And Should Be Withdrawn

The Examiner rejects claims 1 - 11 under 35 U.S.C. § 103 as having been obvious over Cao *et al.*, "5-fluorouracil prodrug: role of anabolic and catabolic pathway modulation in therapy of colorectal carcinoma," *Clin. Cancer Res.* 1:839-845 (1995) (hereinafter, "Cao"). Applicant respectfully traverses the rejection.

Cao describes preclinical studies of the metabolism, chemotherapeutic efficacy, and side effects of ftorafur, alone and in combination with other agents. Ftorafur (Tegafur®) is an orally administrable prodrug of 5-fluorouracil (5-FU), a parenterally administered fluoropyrimidine that has been a mainstay in the chemotherapeutic treatment of epithelial cancers for over 40 years.

Figure 1, adapted from Ichikawa *et al.*,[1] schematizes the basic pathways of fluoropyrimidine anabolic activation and catabolic deactivation.

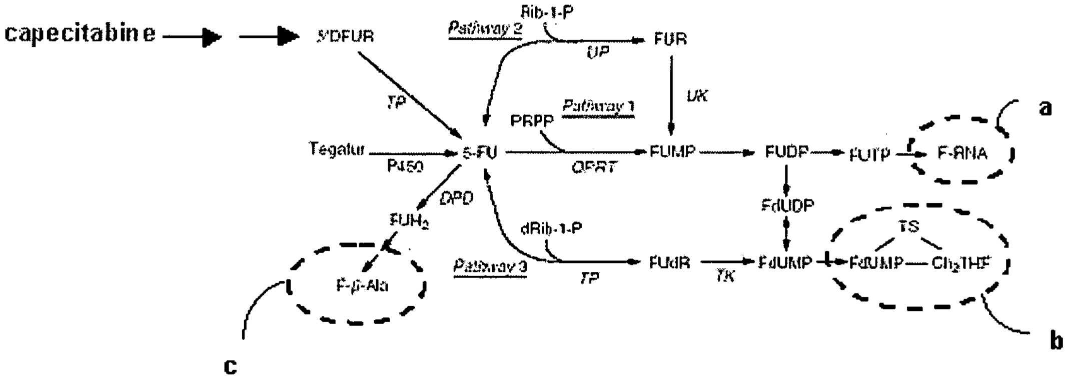

Fig. 1

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[1] Ichikawa *et al.*, "Both gene expression for orotate phosphoribosyltransferase and its ratio to dihydropyrimidine dehydrogenase influence outcome following fluoropyrimidine-based chemotherapy for metastatic colorectal cancer," *Brit. J. Cancer* 89:1486-1492 (2003) (hereinafter "Ichikawa", attached hereto as Exhibit A).

Starting at the middle left of the figure, Tegafur®, administered orally, is converted in the liver to 5-fluorouracil ("FU") by action of cytochrome P450. 5-FU then circulates through the blood and is absorbed from the circulation by cells throughout the body.

Within the cell, 5-FU can be converted to cytostatic (and/or cytotoxic) metabolites by any one or more of three main "anabolic" pathways, each catalyzed by a different enzyme. As labeled in FIG. 1, pathway 1 involves the action of orotate phosphoribosyl transferase (OPRT), pathway 2 activates 5-FU via uridine phosphorylase (UP), and pathway 3 requires the enzyme thymidine phosphorylase (TP). These three pathways interconnect, converging on two principal mechanisms of cell toxicity.

In the first, circled and labeled "a" at the right of FIG. 1, 5-FU is ultimately metabolized to 5-FUTP, which is incorporated during transcription into RNA. Currently, it is thought that the toxicity results from the accumulation of fluorouracil residues in a wide variety of mRNAs coding for many different proteins, rather than from alteration of any single cellular function.[2]

The second principal mechanism of cell toxicity results from anabolic activation of 5-FU to 5-FdUMP. As circled and labeled "b" in FIG. 1, 5-FdUMP forms a ternary complex with thymidine synthase (TS) and the cofactor 5,10-methylene tetrahydrofolate (CH_2THF). Tight complexation sequesters TS, preventing the TS-mediated enzymatic formation of dTMP; this, in turn, decreases the synthesis, and thus availability, of thymidine triphosphate (dTTP), which is required for DNA replication and repair. Depletion of dTTP acts as a cytostatic brake on cell growth and division; more recently, it has been suggested that depletion of dTTP may directly trigger programmed cell death (apoptotic) pathways.[3]

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[2] Malet-Martino *et al.*, "Clinical studies of three oral prodrugs of 5-fluorouracil (capecitabine, UFT, S-1): a review," *The Oncologist* 7:288-323 (2002) (hereinafter, "Malet-Martino", attached hereto as Exhibit B), at p. 291.

[3] Recently, two additional modes of 5-FU cytotoxicity have been suggested: (i) direct incorporation of 5-FU into DNA, causing genetic lesions, and (ii) incorporation of 5-FUDP sugars into membranes and membrane proteins, altering membrane function of 5-FU-treated cells. These putative mechanisms need not be further described here; for present purposes, it suffices to note that the metabolic fate of 5-FU and its metabolites is still under active investigation, more than 40 years after 5-FU's clinical introduction.

Catabolic inactivation of 5-FU is conceptually simpler than anabolic activation, with greater than 80% of an injected dose of 5-FU rapidly degraded by a single pathway, the first and rate-limiting step of which is catalyzed by dihydropyrimidine dehydrogenase (DPD)[4],[5]. The principal byproduct of catabolism, F-β-alanine, is circled and labeled "c" in FIG. 1, above.

Given the complex interrelatedness of the metabolic pathways, the clinical efficacy of 5-FU and its orally-administrable prodrugs depends, to a first, crude, approximation, on the relative activities of the DPD-mediated catabolic pathway and each of the three principal anabolic pathways. But despite intensive study, "**[t]he extent to which any of these pathways predominates in human tumors is unknown and is likely to vary across tumor types and with different modes and doses of drug administration**"[6]; "the contribution of the different pathways to 5-FU activation is still unclear."[7]

The situation becomes more complex when considering the concurrent and interacting effects of multiple, competing, substrates on the multiple and competing catabolic and anabolic enzymes in the fluoropyrimidine pathway.

UFT is a combination of ***u***racil and ***ft***orafur in a 4:1 molar ratio. UFT is approved for clinical use in Europe and Japan; it has been denied FDA approval for clinical marketing in the U.S. for lack of improved efficacy over standard 5-FU/leucovorin.

After oral ingestion, the ftorafur component of UFT is metabolized by P450 to 5-FU. The uracil component is intended to compete with 5-FU for degradation by DPD; present at a several-fold molar excess over ftorafur in the administered composition, and thus intended to be present at a several-fold molar excess over ftorafur (and thus 5-FU) in tissues, uracil is intended to outcompete 5-FU for reaction with DPD, inhibiting DPD catabolic inactivation of 5-FU. The intended result is a higher circulating level of 5-FU, leading to greater 5-FU-mediated cytotoxicity. Cao *et al.*, *Clinical Cancer Res.* 1:839-845 (1995).

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[4] DPD is also known, synonymously, as uracil reductase, dihydrouracil dehydrogenase, and as dihydrothymine dehydrogenase, reflecting the complex interconnections in the pyrimidine metabolic pathways.

[5] It is the high concentration of DPD in the gut that makes oral administration of 5-FU disfavored and motivated the development of orally administrable DPD-resistant prodrugs such as ftorafur (Tegafur®) and capecitabine (Xeloda®).

[6] Malet-Martino at 291 (emphasis added).

[7] Ichikawa at 88.

But the actual *in vivo* concentrations of uracil and 5-FU after UFT administration do not invariably follow the intended ratio. Administration of UFT to rats results in a greater than 100-fold variation in uracil level within various organs, and can lead to up to a 100-fold excess of uracil over 5-FU in some tissues.[8]

Furthermore, uracil can ***also*** compete with 5-FU for reaction with the three principal anabolic activating enzymes. In order for the UFT combination to show greater clinical efficacy than ftorafur alone, uracil must not outcompete 5-FU for activation by at least one of OPRT, TP, and UP in the tumor. The outcome thus depends upon the ***relative amount*** of each of the four principal rate-limiting enzymes in each of the cells and tissues taking up 5-FU, and on the ***relative affinity*** of each of the enzymes for uracil and 5-FU. The latter depends, in turn, at least in part on cellular pH.

Variation in the relative amounts of each of the four principal rate-limiting enzymes among tissues and tumors makes *a priori* prediction of UFT efficacy in any particular tumor unreliable. And experiments in laboratory animals provide little help: the relative affinities of these enzymes for 5-FU and for uracil differ substantially among different animal species, and particularly among different animal tumors and various tumor cell lines.

Sludden *et al.*[9] report, for example, that liver DPD activity is highly variable within and among tested species: "[c]areful selection of preclinical in vivo models is suggested [that is, *recommended*] due to the large variation in DPD activity found in mouse and rat strains in comparison with human liver samples."[10] At least one study reports that "in all [human] tissues tested, 5-fluorouracil is a *better* substrate for dihydrouracil dehydrogenase [DPD] than uracil,"[11] undermining, in part, the rationale for combining uracil with ftorafur in UFT.[12]

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[8] Kawaguchi *et al.*, *Gann.* 71(6):889-99 (1980) (attached hereto as exhibit K)

[9] Sludden *et al.*, "Liver dihydropyrimidine dehydrogenase activity in human, cynomolgus monkey, rhesus monkey, dog, rat and mouse," *Pharmacology* 56:276-280 (1998) (hereinafter "Sludden", attached hereto as Exhibit C).

[10] Sludden *et al.* at 279.

And as complex as the physiology of fluoropyrimidine metabolism may be with respect to desired antitumor effects, the pathophysiology of fluoropyrimidine side-effects is even less well understood.

Among the poorly understood side effects of fluoropyrimidine administration, the physiology of hand-foot syndrome ("HFS", "palmar-plantar erythrodysesthesia", "PPES") is perhaps the most obscure:

- "[t]he specific pathophysiologic mechanism is unknown"[13]
- "[t]he etiopathogenesis of . . . PPES . . . is still unknown . . . , but it has been postulated that the local drug accumulation secondary to different scheduling (continuous infusion instead of bolus infusion), the total amount of drug, alcoholism, local trauma, increased blood flow could be responsible for them"[14]
- "[t]he pathophysiology of HFS is largely unknown"[15]
- "it is clear that catabolic products of the drugs are unlikely to be involved since the exact same syndrome is manifest with two entirely different drug classes (anthracyclines and antimetabolites) with distinctly different catabolism and catabolic products"[16]

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[11] Naguib *et al.*, "Enzymes of uracil catabolism in normal and neoplastic human tissues," *Cancer Research* 45:5405-5412 (1985) (emphasis added) (attached hereto as Exhibit D).

[12] Some data suggest that UFT, which has not been approved by the FDA, is less efficacious than 5-FU in human beings. Wang *et al.*, "Oral 5-FU is a more effective antimetastatic agent than UFT," *Anticancer Res.* 24:1353-60 (2004) (attached hereto as Exhibit E).

[13] Childress and Lokich, "Cutaneous hand and foot toxicity associated with cancer chemotherapy," *Amer. J. Clinical Oncology* 26:435 - 436 (2003) (hereinafter, "Childress", attached hereto as Exhibit F), at 435.

[14] Leo *et al.*, "Dermatological toxicity from chemotherapy containing 5-fluorouracil," J. Chemother. 6:423-426 (1994) (attached hereto as Exhibit G).

[15] Elasmar *et al.*, "Case report: hand-foot syndrome induced by the oral fluoropyrimidine S-1," *Jpn J. Clin. Oncol.* 31:172-174 (2001) (hereinafter "Elasmar", attached hereto as Exhibit H).

[16] Childress, at 435.

- "The pathophysiology of S-1-induced HFS may differ somewhat from that of capecitabine-induced HFS"[17]
- "HFS is . . . attributed to the presence of the main 5-FU metabolites, FUH2 and FBAL, but without strong pharmacological arguments. . . . [Our] data strongly suggest that the presence of 5FU metabolites does not play a major role in the HFS generated by capecitabine and that it can probably be attributed to a particularly high TP activity in keratinocytes."[18]

In the face of such mechanistic uncertainty, the current standard of practice is to reduce the dose of fluoropyrimidine when hand-foot syndrome develops. Unfortunately, the severity of hand-foot syndrome appears to correlate with tumor response:[19] dose attenuation to reduce the symptoms of hand-foot syndrome thus also reduces efficacy of tumor treatment.

The instant inventor has discovered a way to dissociate the anti-tumor effect of systemically administered 5-FU and capecitabine (an oral 5-FU prodrug) from this major toxic side effect. The instant inventor has discovered that local administration of uracil to the sites affected by hand-foot syndrome -- in an amount and by means sufficient to establish a high local concentration of uracil, with the systemic absorption and circulation of uracil insufficient to abrogate the clinical efficacy of the systemically administered fluoropyrimidine -- both prevents the development of hand-foot syndrome and allows re-escalation of the dose of fluoropyrimidine (see Example 1 for evidence of re-escalation of dose of capecitabine), with recovery of the systemic agent's anti-tumor effect. This is a clinically significant achievement.

The Cao *et al.* reference cited by the Examiner neither discloses, teaches, nor suggests such a method: it discusses only alopecia and stomatitis; it makes no mention of local, particularly topical, treatment of side effects of fluoropyrimidine application; and as admitted by the Examiner, "does not teach . . . the topical administration of uracil."[20]

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[17] Elasmar.

[18] Fischel *et al.*, "Experimental arguments for a better understanding of hand-foot syndrome under capecitabine," *Proc. Amer. Ass'n Cancer Res.* 45:487 (abstract #2119) (March 2004) (attached hereto as Exhibit I).

[19] Chua *et al.*, " Efficacy of capecitabine monotherapy in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy," *Proc. am. Soc. Clin. Oncol.* 22:511 (abstr. 2055) (2003) (attached hereto as Exhibit J).

At most, Cao might be said to disclose that "[t]he severe alopecia [hair loss] observed with FT [ftorafur] alone was reduced significantly by [concurrent systemic administration of] uracil [to rats]."[21],[22]

Even that may be an overstatement. Hand-foot syndrome is rarely seen with the ftorafur-containing prodrug combination S-1. S-1 lacks uracil yet, like UFT, causes hand-foot syndrome only rarely. Cao's data are not inconsistent with the ftorafur component being responsible for the low incidence of hand-foot syndrome upon administration of UFT.

It is, of course, axiomatic that the cited reference must teach or suggest all claim limitations. M.P.E.P. § 2143. To remedy the failure of Cao to mention hand-foot syndrome, local treatment of fluoropyrimidine side effects and, in particular, "the topical administration of uracil," the Examiner posits that "the determination of a dosage as well as modes and methods of administration . . . is well within the level of the skilled artisan. Accordingly, one having ordinary skill in the art would be motivated to determine optimum modes of administration, such as topical administration . . . in order to get the maximum effect of the drug."[23]

Applicant respectfully disagrees.

A condition precedent to the Examiner's proposed dose-finding studies is a suggestion or motivation to divorce the route of administration of uracil from that of tegafur; that is, to strip uracil from its combination with ftorafur in UFT, administering the one locally, the other systemically, effectively vitiating the very utility presumed to flow from systemic administration of uracil in admixture with the fluoropyrimidine active.

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[20] Office action at 4.

[21] Cao, abstract. And even that inference is suspect: S-1, a ftorafur-containing combination that lacks uracil, rarely causes hand-foot syndrome, Elasmar, which may suggest that it is the ftorafur component, not the uracil, that accounts for the paucity of hand-foot syndrome reports upon treatment with UFT.

[22] Cao does not address the possibility that administration of uracil at high dose, shown in their data to spare hair loss, might reasonably also be countering, or sparing, the systemic anti-cancer effect of the ftorafur component. By administering uracil orally, Cao may be doing nothing more than reducing the effective dose of ftorafur.

[23] Office action at 4 - 5.

A condition precedent to the Examiner's proposed pharmacologic routineering must be a suggestion that uracil, administered locally, would act to decrease, rather than to increase, the local toxicity of the systemically administered fluoropyrimidine, directly contrary to its presumptive effect in UFT.

Neither such suggestion can be found in Cao.

Nor are such suggestions found elsewhere in the art, dose attenuation being the art-accepted, standard clinical response to development of hand-foot syndrome.

The Examiner must also establish that a reasonable expectation of successfully preventing hand-foot syndrome would have attended the topical application of uracil.

Cao provides no such expectation. Nor is there other evidence of record that would support such proposition.

Indeed, given the uncertainty as to the pathophysiologic basis of hand-foot syndrome; given the complexity of the fluoropyrimidine metabolic pathways; given the variability in relative activities in various tissues of the critical enzymes of fluoropyrimidine catabolism and anabolism; given the variability in relative enzyme affinity for 5-FU and uracil as between laboratory animals and human beings; given the received wisdom that uracil increases fluoropyrimidine activity (that is, cytotoxicity); given the curious infrequency of hand-foot syndrome upon treatment with S-1, a ftorafur prodrug combination lacking uracil, applicant respectfully submits that no such expectation would have been present prior to his invention.

Lacking explicit elements of applicant's claims, providing no evidence of prior art suggestion or motivation to make applicant's invention, and failing to show that the prior art would have provided a reasonable expectation that applicant's inventive methods would successfully prevent or treat hand-foot syndrome, the Examiner's *prima facie* case of obviousness fails. With failure of the *prima facie* case, applicant is entitled, without more, to his patent. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

In addition, applicant respectfully submits that Cao, which teaches the advantage of systemic administration of uracil in combination with, and to increase the cytotoxicity of, ftorafur, teaches away from applicant's invention, the topical administration of uracil to counter cytotoxicity of systemic fluoropyrimidines. This teaching away from applicant's invention is a compelling indicium of nonobviousness.

For the foregoing reasons, applicant respectfully submits that the rejection is in error and should be withdrawn.

The Provisional Obviousness-Type Double Patenting Rejection Has Already Been Obviated

The Examiner provisionally rejects claims 1 - 11 under the judicially created doctrine of obviousness-type double patenting over claims 13 - 47 of parent application no. 10/364,383 ("the '383 application").

The '383 application has been affirmatively abandoned. Applicant respectfully submits that the rejection, having been obviated, should be withdrawn.

CONCLUSION

Applicant submits that the present application is in condition for allowance, and respectfully requests the same. Applicant respectfully requests a **personal interview** with the Examiner should the Examiner find that matters remain outstanding before passing the case to issuance.

Respectfully submitted,

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Enclosures:	Power of Attorney and Correspondence Address Indication Form
	IDS, including PTO-1449 and references
Attachments:	Exhibits A - K